#12 Appeal 3-1-94

CERTIFICATE OF MAILING

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 92,749/D015 US)

In re Application of: Linda C. Burkly	Before the Examiner: L. Feisee
Serial No.: 08/029,330	
Filed: February 9, 1993	Art Unit: 1806
For: TREATMENT FOR INSULIN DEPENDENT DIABETES	

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DECLARATION OF LINDA C. BURKLY

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Linda C. Burkly, residing at 34 Winthrop Street, West Newton, Massachusetts 02165, hereby declare the following:

1. I am the inventor of the subject matter disclosed and claimed in the present U.S. Patent Application.

2. I hold a Ph.D. degree which was conferred to me in March 1985 from Tufts University.

3. I am presently employed as a Scientist in the Department of Immunology at Biogen, Inc. in Cambridge,

Massachusetts and have held this position since January 1989. Prior to this, I was employed as a Post Doctoral Fellow at Biogen for four years.

4. I reviewed the Office Action mailed October 4, 1993 and understand the Examiner's rejections, especially the 35 U.S.C. § 101 rejection concerning the lack of patentable utility.

5. My invention, as presently claimed, relates to a method for preventing onset of insulin dependent (type I) diabetes which comprises administering VLA4 binding agents such as anti-VLA4 antibodies or fragments thereof to a prediabetic subject. The utility of my claimed invention was demonstrated with an adoptive transfer model of diabetes which employs non-obese diabetic (NOD) mice, an art-recognized animal model for human type I diabetes. R1-2, an anti-VLA antibody, was used in these experiments. See Examples 1 and 2 on pages 23-30; page 8, line 28; page 18, lines 8-21; and page 19, lines 29-33.

6. In support of the patentability of my claimed invention, I have included results from two additional experiments which provide further evidence of the asserted utility. In Example No. 3, I evaluated the efficacy of R1-2 in a spontaneous disease model which employs NOD mice. In Example No. 4, I evaluated the efficacy of PS/2, an anti-VLA4 antibody comparable to R1-2, using the same adoptive transfer model described in my application. Details concerning the isolation and purification of PS/2 were reported in the literature (Miyake

et al., J. Exp. Med., 173:599-607, 1991). The results of my experiments are attached as Exhibits A and B.

7. In Example No. 3, NOD mice were treated for 8 weeks with (a) an irrelevant control antibody (NOD/rat IgG2b, n = 10 mice); (b) R1-2 antibody (NOD/R1-2, n = 20 mice); or (c) no treatment (NOD, n = 10 mice) starting at week four through week eleven. Diabetes was monitored by glycosuria each week. Details concerning the dosages, administration routes, and experimental procedure are essentially the same as the ones described in my application. See, for example, page 24, lines 6-22, in the application. The results of this spontaneous disease model experiment are summarized in a figure attached as Exhibit A.

8. Exhibit A figure demonstrates a marked delay in diabetes onset (12-16 weeks delay) in NOD mice following R1-2 administration (▲, NOD/R1-2 mAb), as compared to the two control groups. Control NOD mice which received IgG2b (•, NOD/rat IgG2b) or no treatment (□, NOD) developed diabetes as early as 13 weeks. The inhibition of diabetes results obtained in the spontaneous disease model with R1-2 parallel the adoptive transfer results found in Example No. 1 of the application. See the application at page 9, lines 2-14; page 24, lines 31 and 32; page 25, lines 1-22; and Figures 1 and 2.

9. In Example No. 4, I conducted a comparative adoptive transfer NOD mice experiment with R1-2, PS/2 (an anti-VLA4 antibody which exhibits pharmacokinetics comparable to R1-2), and

an irrelevant antibody IgG2b. Recipient mice receiving NOD donor cells (D), non-NOD donor cells (non-D) and no cells (NONE) served as controls for this experiment. The protocol and dosage amounts for this adopted transfer model experiment are the same as the one described in the application. See, for example, page 23, lines 4-32 and page 24, lines 1-22 in the application. The evaluation results are summarized in Table I (attached as Exhibit B).

10. Exhibit B Table summarizes the diabetes incidence in NOD mice treated with either R1-2 (D/R1-2 mAb), PS/2 (D/PS/2 mAb) or IgG2b (D/IgG2b). As expected, control recipients of splenocytes from non-diabetic mice (Non-D) or of PBS alone (NONE) essentially failed to become diabetic. Both R1-2 and PS/2 substantially inhibit development of overt diabetes during four weeks post-transfer. In contrast, diabetes occurred at high incidence (84% of total recipients) and generally between 2-3 weeks post-transfer in D and D/rat IgG2b mice. Thus, mAbs directed against the VLA4 molecule specifically protects against transfer of autoimmune diabetes.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may

jeopardize the validity of the application or any patent issuing thereon.

2/3/94
Date of Signature

Linda C. Burkly
Linda C. Burkly

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